#2

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and provisional specification filed on 02.09.2002 in respect of Patent Application No. 790/MUM/2002 of Sun Pharmaceutical Industries Ltd., Acme Plaza, Andheri-Kurla Road, Andheri (E),Mumbai – 400059, India, an Indian Company.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

Dated this 6th day of November 2003

M. A. Haafeez.

(M.A. HAAFEEZ)
ASST. CONTROLLER OF PATENTS & DESIGNS

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

FORM 1

THE PATENTS ACT, 1970
(39 OF 1970)

APPLICATION FOR GRANT OF A PATENT
(See sections 5(2), 7, 54 and 135 and rule 33A)

We, SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, MAHARASHTRA, INDIA

AN INDIAN COMPANY

hereby declare -

(i) that we are in possession of an invention titled **"PROCESS FOR THE PREPARATION OF A PHARMACEUTICAL COMPOSITION OF METAXALONE WITH ENHANCED BIOAVAILABILITY".**

(ii) that the provisional specification relating to this invention is filed with this application.

(iii) that there is no lawful ground of objection to the grant of a patent to us.

We, further declare that the inventors for the said invention are
Dr. Nitin Bhalachandra Dharmadhikari & Mr. Ashish Prabhakar Mungre all of SUN PHARMACEUTICAL ADVANCED RESEARCH CENTRE LIMITED, Bombay College of Pharmacy Building, 2nd Floor, C.S.T. Road, Kalina, Mumbai 400098, Maharashtra, INDIA; all Indian nationals.

We claim the priority from the applications filed in convention countries, particulars of which are as follows: Not Applicable

We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: Not Applicable

We state that the application is divided out of our application, the particular of which are given below and pray that this application deemed to have been filed under section 16 of the Act: Not Applicable

That we are the assignee of the true and first inventors.

That our address for service in India is as follows-

Dr. RATNESH SHRIVASTAVA,
INTELLECTUAL PROPERTY CELL,
SUN PHARMACEUTICAL INDUSTRIES LTD,
ACME PLAZA, ANDHERI-KURLA ROAD,
ANDHERI (E), MUMBAI-400 059, INDIA,
TELEPHONE NO-8397632, FACSIMILE NO- 8212010.

790/mum/2002
2/9/2002

Following declaration was given by the inventors-
We, the true and first inventors for this invention declare that the applicant herein is our assignee.

Dated this 30th day of August, 2002.

(Signatures) 1. N.B. Dharmadhikari

Dr. Nitin Bhalachandra Dharmadhikari

2. Amgre

Mr. Ashish Prabhakar Mungre

That to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of a patent to us on this application.

Following are the attachment with the application:

1) Provisional specification (3 copies)
2) Fee Rs.5000/- in cheque bearing No. 658714 dated 23/08/2002 on Bank of Baroda.

We request that a patent may be granted to us for the said invention

Dated this 30th day of Aug, 2002.

(Signature) .....

DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LTD.

To

The Controller of Patents,
The Patent Office,
Mumbai - 400 013.

FORM 2

THE PATENTS ACT, 1970
(39 OF 1970)

PROVISIONAL SPECIFICATION
(See section 10)

"PROCESS FOR THE PREPARATION OF A PHARMACEUTICAL COMPOSITION OF METAXALONE WITH ENHANCED BIOAVAILABILITY"

SUN PHARMACEUTICAL INDUSTRIES LTD.

A company incorporated under the laws of India having their office at ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, MAHARASHTRA, INDIA.

The following specification describes the nature of this invention.

" PROCESS FOR THE PREPARATION OF A PHARMACEUTICAL COMPOSITION OF METAXALONE WITH ENHANCED BIOAVAILABILITY "

The present invention relates to a process for the preparation of a pharmaceutical composition of metaxalone with enhanced bioavailability. The present invention further relates to a process for the preparation of a pharmaceutical composition of metaxalone with enhanced bioavailability such that, the bioavailability is not significantly affected by presence of food.

BACKGROUND OF THE INVENTION:

Metaxalone, [5-(3,5-Dimethylphenoxymethyl)-2-oxazolidinone] disclosed in the United States Patent No. 3,062,827 is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculo-skeletal conditions. Metaxalone is therapeutically categorized as a skeletal muscle relaxant. Its mechanism of action in humans has not been well established, but may be due to general central nervous system depression. Metaxalone does not directly relax tense muscles in man. The recommended dose of metaxalone for adults and children over 12 years of age is two tablets (800 mg) three to four times daily.

United States Patent No. 3,062,827 discloses crystalline metaxalone with a melting point of 121.5-123°C. Metaxalone, being a hydrophobic molecule, has low aqueous solubility.

United States Patent No. 6,407,128 discloses methods of increasing the oral bioavailability of metaxalone by administration of an oral dosage form with food in human subjects. Preferably the invention describes administration of the dosage form between 30 minutes prior, to 2 hours after consuming solid food with sufficient bulk and fat content that is not rapidly dissolved and absorbed in the stomach. Thus, in the disclosed invention, a method of increasing rate and extent of metaxalone absorption is provided comprising administering the therapeutically effective amount of metaxalone in the formulation of the drug product Skelaxin® to the patients with food.

Thus, the prior art discloses that metaxalone has low aqueous solubility, a high dose and its bioavailability is affected by the presence of food. These factors point towards a bioavailability, which is limited by the ability of the pharmaceutical composition to release mataxalone at a rapid rate in an absorbable form, however, the prior art does not provide a pharmaceutical composition of metaxalone with enhanced or improved bioavailability. Enhanced bioavailability of drug substance is known to increase both onset of action and therapeutic efficacy. Hence, it is desirable to provide metaxalone in a pharmaceutical composition with enhanced bioavailability as compared to commercially available pharmaceutical composition of metaxalone. The prior art also does not provide a pharmaceutical composition of metaxalone whose bioavailability is independent of whether the patient takes the composition on an empty stomach or with food. The desired bioavailability is exceeded if the patient takes the composition with food exposing the patient to higher blood level and amounts of metaxalone. Thus it would be desirable to find a composition of metaxalone whose bioavailability is not significantly affected by food.

OBJECTS OF THE INVENTION

It is the object of the present invention to provide a process for the preparation of a pharmaceutical composition comprising metaxalone and pharmaceutically acceptable excipients, characterized in that the pharmaceutical composition has enhanced bioavailability.

A further object of the invention is to provide a process for the preparation of a pharmaceutical composition comprising metaxalone and pharmaceutically acceptable excipients, characterized in that the bioavailability is not significantly affected by presence of food.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 shows the plasma concentration vs. time profile obtained upon administration of an embodiment of the pharmaceutical composition of the present invention having 400 mg metaxalone in comparison to that obtained from an equivalent dose of a conventional pharmaceutical composition available commercially.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process for the preparation of a pharmaceutical composition comprising metaxalone and pharmaceutically acceptable excipients, characterized in that the pharmaceutical composition has an enhanced bioavailability as compared to the conventional pharmaceutical compositions of metaxalone known in the art.

In preferred embodiment, the present invention further provides a process for the preparation of a pharmaceutical composition of metaxalone, where bioavailability is not significantly affected by presence of food. The bioavailability of known conventional pharmaceutical composition of metaxalone available commercially is known to be affected by presence of food.

Metaxalone that may be used in the process of the present invention may be micronized metaxalone obtained either by the final step during the manufacture of metaxalone or by the use of conventional micronizing techniques after the conventional crystallization procedure. Where micronization techniques are employed, metaxalone may be micronized to the desired particle size range by conventional techniques known in the art like for example, using a ball mill, rod mill, hammer mill, cutter mill, fluid energy attrition mill, jet mill, chaser mill, centrifugal-impact mill, roller mill, colloidal mill, microfluidizer, homogenizers, ultrasonic means and the like. The milling may be dry or wet milling of metaxalone in the absence or in the presence of a pharmaceutically acceptable excipients.

Particle size distribution of metaxalone and values determined thereupon as referred to herein are those derived from measurement using a Sympatec HELOS (H0899) particle size analyzer, however, these may be measured by any suitable technique. Typically, the volume size distribution of the metaxalone that may be used in the present invention is given in Table 1 below.

Table 1

% Undersize	Preferred	More Preferred	Most Preferred
99 %	NMT* 40 μm	NMT 20 μm	NMT 10 μm
90 %	NMT 30 μm	NMT 14 μm	NMT 6 μm
50 %	NMT 10 μm	NMT 5 μm	NMT 3 μm

*NMT = Not More Than

The metaxalone used in the pharmaceutical composition of the present invention has a specific surface area per unit volume more than about 1.5 m^2/cm^3 preferably more than about 2.5 m^2/cm^3. In highly preferred embodiment the specific surface area per unit volume is equal to or more than about 3.0 m^2/cm^3.

Metaxalone may be used in the pharmaceutical composition of the present invention in the range of amounts equivalent to about 400 mg to about 1600 mg of metaxalone. In particular the pharmaceutical composition of the present invention may have metaxalone in an amount equivalent to 400 mg of metaxalone.

The pharmaceutical composition of the present invention may be formulated into any suitable dosage form, such as tablets, capsules, pills, lozenges, granules, powders, pellets, liquids, emulsion, suspension, elixir and the like. The pharmaceutically acceptable excipients may be any pharmaceutical excipient that would function as carrier materials, bulking agents, binders, lubricants, buffer, surfactant, diluent, disintegrant, glidant, colouring agent and the like.

Pharmaceutically acceptable excipients that may be used in the present invention may be selected from those referred to in Handbook of Pharmaceutical Excipients: third edition Ed. Arthur H. Kibbe; American Pharmaceutical Association, Washington D.C. (2000) as well as in Remington: The Science and Practice of Pharmacy, edition 20, Lippincott Williams and Wilkins, Philadelphia (2000).

One embodiment of the process of the present invention comprises mixing of micronized metaxalone and pharmaceutically acceptable excipients, for example, binders such as cellulose derivatives, starch, gelatin, sugars, polyvinyl pyrrolidone and the like, disintegrants such as starch, modified starch such as sodium carboxy methyl starch, cellulose derivatives, natural and synthetic gums and the like, lubricants such as talc, magnesium stearate colloidal silicon dioxide, poly ethylene glycol and mixtures thereof, wetting agents such as polyols, surfactants and the like, additionally colouring agents including food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminium oxide and formulating into a suitable dosage form by conventional means well known to the person skilled in the art.

In another embodiment of the process of the present invention, the metaxalone and a pharmaceutically acceptable excipient are together subjected to milling by conventional techniques known in the art like for example, using a ball mill, rod mill, hammer mill, cutter mill, fluid energy attrition mill, jet mill, chaser mill, centrifugal-impact mill, roller mill, colloidal mill, microfluidizer, homogenizers, ultrasonic means and the like and formulated into a suitable dosage form by conventional means well known to the person skilled in the art.

When the pharmaceutical composition of the present invention is formulated into tablets, methods that are well known to those skilled in the art are used such that the tablets readily disintegrate into granules which then readily disintegrate into easily wettable microparticles in order to effectively expose the surface of metaxalone to the surrounding gastro-intestinal fluids or alternatively the tablets rapidly erode exposing easily wettable microparticles. Factors affecting such performance of tablets are well known to those skilled in the art and include for example hardness of tablets, amounts and type of binding, disintegrating and lubricating agents used, use of wetting agents, moisture content of the granules etc. Preferably the composition of the present invention includes a wetting agent to improve the wettability of the metaxalone microcrystals. Preferably the wetting agent is an orally pharmaceutically acceptable excipient such as a polyol like polyethylene glycol and the like and surfactants such as nonionic, ionic surfactants, polyoxyethylene sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene stearates, poloxamers and the like, and any other wetting agent known in the art. More preferably the surfactant is sodium lauryl sulfate.

The pharmaceutical composition as herein described is orally administered to humans on an empty stomach or with meals and is characterized in that the pharmaceutical composition has an enhanced bioavailability as compared to conventional pharmaceutical composition of metaxalone available commercially. In a preferred embodiment, the pharmaceutical composition is such that the bioavailability is not significantly affected by presence of food. Bioavailability referred to here is rate and extent to which the active drug ingredient, metaxalone, is absorbed into the systemic circulation from the pharmaceutical composition of the present invention.

Example 1

This example illustrates one embodiment of the process for the preparation of a pharmaceutical composition of metaxalone. Tablets were prepared as per the formula given in Table 2 below.

Table 2

Sr. No	Ingredients	Quantity [mg/(percent weight) of the tablet]
Stage A		
1.	Metaxalone (micronized)	400.0/(86.96)
2.	Hydroxypropyl methyl cellulose E15LV	4.00/(0.87)
3.	Pregelatinised starch (Starch 1500)	30.00/(6.52)
4.	Iron oxide red	0.3/(0.065)
Stage B		
1.	Sodium lauryl sulfate	0.60/(0.13)
2.	Hydroxypropyl methyl cellulose E15LV	2.50/(0.54)
Stage C		
1.	Colloidal Silicon dioxide	0.75/(0.163)
2.	Corn starch (dried)	16.35/(3.55)
3.	Magnesium stearate	5.50/(1.19)

Metaxalone was micronized using a jet mill (MIDAS micronizer, M-200). Volume size distribution of the milled metaxalone as determined by Sympatec HELOS (H0899) particle size analyzer is given in Tables 3 and 4 below.

Table 3

Sr. No.	Cumulative % Undersize	Size (μm)
1	36.67	1.80
2	45.83	2.20
3	53.91	2.60
4	60.94	3.00
5	69.92	3.60
6	79.39	4.40
7	86.29	5.20
8	92.06	6.20
9	96.07	7.40
10	98.12	8.60
11	99.23	10.00
12	99.80	12.00
13	100.00	15.00

Table 4

Sr. No.	Cumulative % Undersize	Size/diameter (μm)
1	50% (d50)	2.41
2	75% (d75)	4.03
3	90% (d90)	5.84
4	95% (d95)	7.08
5	97% (d97)	7.95
6	99% (d99)	9.71

Tablets were prepared as per the following procedure.

Stage A: Hydroxy propyl methyl cellulose E15LV, pregelatinised starch and iron oxide red were mixed together and passed through # 60 sieve (as defined by American Society for Testing and Materials, ASTM). Metaxalone (micronized) was mixed well with the above mix. Stage B: Sodium lauryl sulfate was dissolved in distilled water and added to the blend of stage A while mixing. Hydroxy propyl methyl cellulose E15LV dispersed in distilled water was used to granulate the powder blend. The granules were dried in fluid bed dryer and passed through a mill. Stage C: A mixture of starch, magnesium stearate and colloidal silicon dioxide, passed through a # 60 sieve, was then used to lubricate the dry granules. This lubricated mass was then

compressed at a weight of 460 mg using 11.0 mm beveled edged round punches to obtain the final tablets.

The tablets were tested for disintegration time as per standard procedure described in Indian Pharmacopoeia. It was observed that the tablet completely eroded in the disintegration medium in about 30 minutes into microparticles.

The tablets so obtained were subjected to dissolution testing using United States Pharmacopoeia type II dissolution apparatus at 75 rpm. The dissolution medium used was 900ml of 1% sodium lauryl sulfate solution. The results of the dissolution test are mentioned in Table 5 below.

Table 5

Time (minutes)	% drug released (±SD)
15	23 ± 3.5
30	44 ± 6.44
60	71 ± 7.34
120	98 ± 2.58

It was observed that the tablet completely eroded in the dissolution medium in about 60 minutes into microparticles.

Example 2

The bioavailability of the pharmaceutical composition according to the process of the present invention (400 mg metaxalone tablets) and that of conventional pharmaceutical composition of metaxalone available commercially (Skelaxin®, 400 mg tablets) were studied. A single-dose, open label, randomized, comparative and two-way crossover pharmacokinetic study with a seven day washout period, was undertaken for the same.

Metaxalone (SPARC, Mumbai, Lot no. M274-3D, Mfg. Date : March 2001) 400 mg tablets was used as the test product and Skelaxin (Carnrick Lab Inc., USA, Lot no. GS 1043A, Exp. Date : Oct 2003) 400 mg tablets was used as the reference product.

The pharmacokinetic assessment was based on the plasma levels of metaxalone measured by blood sampling. Blood samples were obtained before dosing and at the following times after administration of both the reference and test medications at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 36 and 48 hours

Nine healthy male volunteers were enrolled for the study and all of them completed the two-way crossover study. The subjects were fasted overnight before dosing and for 4 hours thereafter. Drinking water was prohibited 2 hours before dosing and 2 hours thereafter. Standard meals were provided at 4 hours and 8 hours after dosing and at appropriate times thereafter. Meal plans were identical for both the periods.

Subjects received a single conventional tablet of metaxalone (400 mg) as the test product, and single conventional tablet of Skelaxin (400 mg) as the reference product with 240 ml of drinking water at ambient temperature after the overnight fast.

The plasma concentration of metaxalone was determined for samples collected at different time points and averaged over the nine volunteers. The data is given in Table 6 below. The plasma concentration versus time profile is illustrated in Figure 1.

Table 6

Time (hrs)	Mean Plasma Concentrations (ng/ml)	
	Metaxalone 400 mg tablets (Test product)	Skelaxin 400 mg tablets (Reference product)
0.0	0.00	0.00
0.5	0.00	0.00
1.0	367.63	191.26
1.5	604.73	413.47
2.0	1098.11	380.88
2.5	1196.08	449.43
3.0	1034.09	484.45
3.5	982.32	566.00
4.0	951.62	606.26
4.5	901.85	574.38
5.0	859.79	659.52
6.0	655.77	511.94

8.0	324.92	350.78
12.0	203.37	218.48
16.0	107.00	147.98
24.0	0.00	28.35
36.0	0.00	0.00
48.0	0.00	0.00

The pharmacokinetic parameters calculated using the Win Nonlin software are given in Tables 7 and 8 below.

Table 7

Untransformed				
Parameter	**Units**	**Least Square Means**		**Ratio (%T/R)**
		Skelaxin Tablets (Reference product)	**Metaxalone Tablets (Test product)**	
C_{max}	ng/ml	982.44	1418.56	144.39
AUC_{0-t}	hr*ng/ml	5594.83	7176.69	128.27
AUC_{0-inf}	hr*ng/ml	6890.74	8507.94	123.47
T_{max}	hr	3.50	2.44	69.71

Table 8

Ln-transformed				
Parameter	**Units**	**Least Square Means**		**Ratio (%T/R)**
		Skelaxin Tablets (Reference product)	**Metaxalone Tablets (Test product)**	
C_{max}	ng/ml	825.60	1355.21	164.15
AUC_{0-t}	hr*ng/ml	4518.61	6012.08	133.05
AUC_{0-inf}	hr*ng/ml	5719.94	7110.43	124.31
T_{max}	hr	3.07	2.31	75.24

As is evident from the table the metaxalone composition according to the process of the present invention gave significantly higher peak plasma concentration which was achieved more rapidly than with the reference product. The bioavailability as measured by the area under the plasma concentration –time profile was significantly higher for the pharmaceutical composition of the present invention as compared to the reference product.

While the invention has been described with reference to specific embodiments, this was done for purposes of illustration only and should not be considered to limit the spirit or the scope of the invention.

Dated this 30th August, 2002.

DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR,
SUN PHARMACEUTICAL INDUSTRIES LTD.

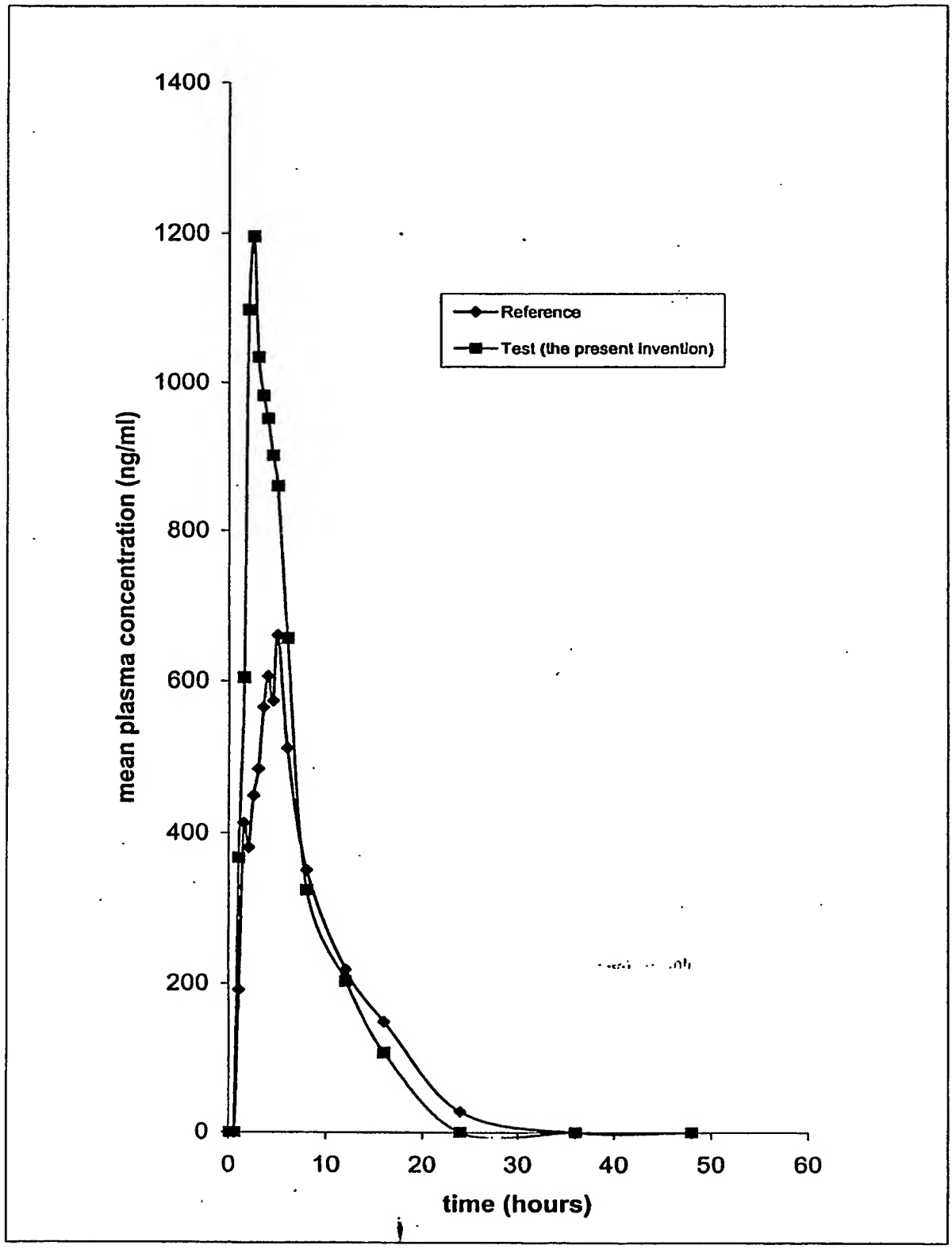

FIGURE 1

12 SEP 2002

DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR